DETAILED ACTION

The office acknowledges the receipt of the amendments and the remarks from the Applicants received on 3/12/2010. Claims 1, 5-13 have been cancelled. Claims 2-4 have been amended and claims 14-16 have been added new. Claims 2-4, 14-16 are pending and are being examined on the merits herein.

Response to Remarks/Amendments

Applicants' cancellation and amendment of claims necessitated the withdrawal of 112(1) enablement rejection of claims 1-6, 10 and 11. Applicants' arguments have been fully considered but found not to be persuasive regarding 103(a) rejections. Applicants' addition of new claims and amendments necessitated the new and modified rejections presented in this action. Accordingly, the action is made Final.

Claim Rejections-35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 14, 15, 2-4 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for co-administration of 25 mg 3-oxo-4-aza-7.beta.-methyl-16.beta.-(4-methylphenoxy)-5.alpha.-androst-1- ene and 5 mg 17.beta.-(N-tert-butylcarbamoyl)-3-oxo-4-aza-5.alpha-androst-1-en-3-one (finasteride) (Example 4 in specification), N-(2,5-bis-trifluoromethyl-phenyl)-3-oxo-4-aza-4-methyl-5 alpha-androst- 1-ene-17 beta-carboxamide (dutasteride) (Example 5 in specification), N-(2-trifluoromethyl-phenyl)-3-oxo-4-aza-4-methyl-5 alpha-androst-1-ene- 17.beta-

carboxamide (Example 6 in specification), 25 mg 3-oxo-4-aza-7.beta.-methyl-16.beta.-(4-methylphenoxy)-5.alpha.-androst-1- ene (Example 7 in specification) in treating abdominal obesity and the prior art being enabling for administration of testosterone to middle-aged men and reporting the associated effects that include decreased visceral fat and glucose concentrations and increased insulin sensitivity does not reasonably provide enablement for treating metabolic syndrome with all the pro-drugs of testosterone as claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. See M.P.E.P. 2164.08. The reference of Meyer, J, Pharmacokinetics and Biopharmaceutics, 24, pp. 449-459, is used in this rejection.

The factors to be considered in determining whether a disclosure meets the enablement requirements of 35 U.S.C. 112, first paragraph, have been described in In re Wands, 858 F.2d 731,8 USPQ2d 1400 (Fed. Cir., 1988). The court in Wands states, "Enablement is not precluded by the necessity for some experimentation, such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'" (Wands, 8 USPQ2sd 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (Wands, 8 USPQ2d 1404). Among these factors are: (1) the nature of the invention; (2) the breadth

of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7)the presence or absence of working examples; and (8) the quantity of experimentation necessary

While all of these factors are considered, a sufficient amount for a prima facie case is discussed below.

(1)/(2) The Nature of the Invention and Breadth of the Claims:

The rejected claims are drawn to a method of treating visceral adiposity and metabolic syndrome comprising administering compounds of formula I, III and IV as claimed in claim 1 of the instant application. The claims are very broad with respect to the compounds claimed for the treatment and also with respect to testosterone analogs, precursors, prodrugs etc.

(3)/(4) Guidance of the Specification and Working Examples

The specification provides guidance and working examples related to preparation of Human Prostatic and Scalp 5.alpha.-Reductases, 5.alpha.-Reductase Assay, inhibition Studies of the reductase enzyme, treatment with immunosuppressant cholesterol lowering agents in patients with coronary heart disease (CED) and/or atherosclerotic disease, administration of finasteride in combination with 3-oxo-4-aza-7.beta.-methyl-16.beta.-(4-methylphenoxy)-5.alpha.-androst-1- ene (Example 4 in specification), N-(2,5-bis-trifluoromethyl-phenyl)-3-oxo-4-aza-4-methyl-5 alpha-androst-1-ene-17 beta-carboxamide (dutasteride) (Example 5 in specification), N-(2-trifluoromethyl-phenyl)-3-oxo-4-aza-4-methyl-5 alpha-androst-1-ene- 17.beta-

carboxamide (Example 6 in specification), 25 mg 3-oxo-4-aza-7.beta.-methyl-16.beta.-(4-methylphenoxy)-5.alpha.-androst-1- ene (Example 7 in specification) in treating abdominal obesity. The specification in para 008 states that U.S. Pat. Nos. 5,719,158; 5,739,137; 5,910,497; and 6,001,844 and WO 97/10217 and WO 99/22728 disclose additional 5alpha-reductase inhibitors. The specification does not teach or show any combination therapy of any of the compounds with testosterone or testosterone analog or prodrugs. The specification does not show at what dosages of these compounds in combination with testosterone can be effective in treating the conditions claimed. The specification is not adequately enabled to show how to make prodrugs of testosterone or using prodrugs of testosterone along with the compounds claimed in claim 1 in treating metabolic syndrome disorder.

(5)/(6) State of the Art and Predictability of the Art:

The state of the art and the predictability of the art as stated above in the 112(1) enablement rejection. The state of the prodrug art is summarized by Wolff, Manfred E., Burger's Medicinal Chemistry and Drug Discovery, Fifth Ed., Vol. 1: Principles and Practice, John Wiley & Sons, 1995,975. The table on the left side of page 976 outlines the research program to be undertaken to find a prodrug. The Second paragraph in section 10 and the paragraph spanning pages 976-977 indicate the low expectation of success. In that paragraph the difficulties of extrapolating between species are further developed. Since the prodrug concept is a pharmacokinetic issue, the lack of any standard pharmacokinetic protocol discussed in the last sentence of this paragraph is particularly relevant. Banker, Gilbert S. et al., Modem Pharmaceutics, Marcel Dekker,

New York, 1996, in the first sentence, third paragraph on page 596 states that "extensive development must be undertaken" to find a prodrug. It is well-established that "the scope of enablement varies inversely to the degree of unpredictability of the factors involved", "and physiological activity is generally considered to be an unpredictable factor." In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Finding a prodrug is an empirical exercise. Predicting if a certain ester of a claimed alcohol, for example, is in fact a prodrug, and produces the active compound metabolically, in man, at a therapeutic concentration and at a useful rate, is filled with experimental uncertainty. Although attempts have been made to predict drug metabolism de novo, this is still an experimental science. For a compound to be a prodrug, it must meet three tests. First, the prodrug must itself be biologically inactive. Second, the prodrug must be metabolized to a second substance in a human at a rate and to an extent to produce that second substance at a physiologically meaningful concentration. Thirdly, that second substance must be biologically active.

(7) The relative skill of those in the art:

The relative skill of those in the pharmaceutical development and medical treatment arts is high, requiring advanced education and training.

(8) The Quantity of Experimentation Necessary:

Considering the state of the art as discussed by the references above, and the high unpredictability in the art as evidenced therein, and the lack of guidance provided in the specification, one of ordinary skill in the art would be burdened with undue experimentation to practice the invention commensurate in the scope of the claims. Not

all prodrugs of testosterone would be expected to be as effective as testosterone itself. As such, one of ordinary skill in the art would be burdened with undue experimentation to determine specifically which prodrug would be effective and safe for treating metabolic syndrome disorder. Substantial and undue experimentation would be needed to practice Applicant's invention because the specification lacks sufficient detail to show how to make and use the prodrugs of testosterone in treating metabolic syndrome disorder. In view of the above factors one having ordinary skill in the art would have to undergo an undue amount of experimentation to make the instantly claimed invention commensurate in scope with the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 14-16, 2-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Roehrborn et al. (Urology, 62, 2003, p 894-899) and McConnell et al. (Applicants'

cited IDS: J of Clin Endocrinology and Metabolism, 74, 3, 1992, 505-508) in view of Bhasin et al. (Applicants' cited IDS: Clinical Infectious Diseases, 2003, 37, S142-S149) and Boyanov et al. (Applicants' cited IDS: The Aging Male, 2003, 6, 1-7).

Roehrborn et al. teaches the effects of finasteride on serum testosterone and body mass index in men with benign prostatic hyperplasia. The reference teaches that finasteride, a selective inhibitor of type II alpha reductase, increases the serum testosterone level and decreases the conversion of endogenous testosterone to dihydrosterone (DHT) (see Abstract, introduction, para 1). Also, the reference reports that the larger testosterone increase is seen in finasteride-treated patients in the lower baseline testosterone tertiles ranging from 0.6-0.8 kg/m^2. It is well known that bbody mass index (BMI) is the most widely used measure to diagnose obesity. The reference teaches administration of finasteride to patients with serum testosterone level of <=330 ng/dL (table 1).

McConnell et al. teaches finasteride, an inhibitor of 5-alpha reductase suppresses prostatic dihydrotestosterone in men and increase in testosterone concentration (see abstract, fig.1, 2). The reference teaches decrease in concentration of dihydrotestosterone to 1.14+/-0.3 nmol/kg after finasteride administration and the placebo group had a mean dihydrotestosterone level of 10.3+/-0.6 nmol/kg. The results teaches a reduction of about 30% or more upon administration of finasteride.

The references do not teach the compounds to be useful in the treatment of a male subject with metabolic syndrome (elected species).

Bhasin teaches the effects of testosterone administration on fat distribution, insulin sensitivity and atherosclerosis progression (see Abstract). The reference teaches that testosterone administration to middle-aged men is associated with decreased visceral fat and glucose concentrations and increased insulin sensitivity (see Abstract).

Boyanov etal. teaches that supplementation of testosterone in men with type 2 diabetes, visceral obesity and partial androgen deficiency improved several features of the metabolic syndrome, including glucose homeostasis and body composition (decrease in visceral obesity) and improved symptoms of androgen deficiency (see Abstract, p4, Table 1, p 6, col. 2 para 4). Boyanov teaches a reduction in the waist hip ratio of the patients after month 3 (Table 1). The reference in the Results section reports that waist-hip ratio decreased by 3.96% in the TU-treated group and body fat decreased by 5.6%.

It would have been obvious to one of ordinary skill in the art at the time of the invention to have used 5-alpha reductase inhibitor compound such as finasteride in the treatment of a male subject with metabolic syndrome because of the teachings of Roehrborn, McConnell, Bhasin and Boyanov etal. Roehrban et al. teaches finasteride, an alpha 5- reductase inhibitor increases the serum testosterone level, decreases DHT level and further teaches that finasteride treatment led to significant mean reduction in the body mass index. Bhasin and Boyanov et al. teach the effects and benefits of testosterone administration to male subjects. The references teaches that supplementation of testosterone hormone is beneficial in the treatment of type II diabetes, visceral obesity, metabolic syndrome etc. The 5-alpha reductase inhibitor

compounds inhibit the reductase enzyme thus maintaining the levels of testosterone before they bind to the enzyme and get converted to DHT. Accordingly, it would have been obvious to one having ordinary skill in the art to use finasteride in treating metabolic syndrome because the prior art teaches that administration of finasteride increases the amount of testosterone and testosterone administration to middle-aged men is associated with decreased visceral fat and glucose concentrations and increased insulin sensitivity. One having ordinary skilled in the art would have been motivated to use finasteride and add testosterone as a second agent in treating metabolic syndrome in expectation of therapeutic benefits in attaining decreased visceral adiposity, glucose concentrations and increased insulin sensitivity.

The above said references do not teach that the waist circumference of the male subject to be greater than 102 cm.

. It would have been obvious to one of ordinary skilled in the art at the time of the invention to treat male patients with a waist greater than 102 cm with a compound such as finasteride because waist circumference is a common measure used to assess abdominal fat content and is associated with obesity. The prior art teaches administration of finasteride increases serum testosterone and testosterone has been shown to be associated with decreased visceral fat and glucose concentrations and increased insulin sensitivity and the prior art reports the reduction of waist to hip ratio upon administration of testosterone. One having ordinary skill in the art would have been motivated to select a male patient with a waist greater than 102 cm for treating

metabolic syndrome administering a compound such as finasteride in order to decrease the abdominal fat.

Response to Arguments

(1) 112(1) rejection:

Applicants' argue that given that by definition, a testosterone prodrug releases testosterone, Applicants have retained testosterone prodrugs. In response, Applicants' claim encompass all testosterone prodrugs currently available and yet to be discovered. As stated above in the rejection, finding a prodrug is an empirical exercise. Predicting if a certain ester of a claimed alcohol, for example, is in fact a prodrug, and produces the active compound metabolically, in man, at a therapeutic concentration and at a useful rate, is filled with experimental uncertainty. Although attempts have been made to predict drug metabolism de novo, this is still an experimental science. For a compound to be a prodrug, it must meet three tests. First, the prodrug must itself be biologically inactive. Second, the prodrug must be metabolized to a second substance in a human at a rate and to an extent to produce that second substance at a physiologically meaningful concentration. Thirdly, that second substance must be biologically active. . Not all prodrugs of testosterone would be expected to be as effective as testosterone itself. As such, one of ordinary skill in the art would be burdened with undue experimentation to determine specifically which prodrug would be effective and safe for treating metabolic syndrome disorder. It would be an undue experimentation to a person of ordinary skill in the art to make a prodrug of testosterone and test in vitro and then in

vivo to evaluate the therapeutic concentration useful for treating metabolic syndrome. Accordingly, the rejection is maintained.

(2) 103(a) rejection:

Applicants argue that the invention is surprisingly advantageous in terms of the improved safety and is also surprising because the art teaches away from the use of the combination of the invention. Applicants' have cited the following teachings from the literature articles: (1) administration of testosterone results in DHT (dihydrotestosterone, DHT) - Marks 2006 and Page et al. 2006 (2) Added risk of prostate cancer attributable to the increase of DHT, Kaplan et al. 2009 (3) men with metabolic syndrome are at risk of prostate cancer (4) Impotence is the common adverse reaction for finasteride, dutasteride drugs. In response, Marks 2006 teaches in page 2357, under Prostate Cancer, that 6 out of 41 men who completed the trial were found to have prostate cancer on the biopsy performed at the end of the study; 4 of19 (21%) in the placebo group and 2 of 21 (9.5%) in the TRT group. In addition, in p 2358, in the comments section Mark describes that “exogenous testosterone when administered for 6 months to men with symptomatic hypogonadism in dosages sufficient to increase serum testosterone levels to the mid-normal range appears to have little effect on the prostate gland, prostate androgen levels were increased only slightly, prostate tissue composition, and biomarkers of cell proliferation and angiogenesis were not altered, gene expression was not changed”. Furthermore the reference in p 2359, col. 1, lines 1-4 states that “therefore under the conditions herein including the biopsy to detect cancer performed pretreatment, a degree of prostate safety is defined for men undergoing

TRT". In p 2359, col. 3, the reference discusses the teachings of Rhoden and Morgentaler, "showed that even in men with a predisposition to prostate cancer, 1 year of TRD did not increase cancer incidence". In addition in p 2360, line 20, the reference states that "From these data, TRT cannot be implicated as a cancer stimulus". Also, in p 2360, col. 2, para 3, the reference teaches that "the benefits of short-term androgen administration in patients with metabolic syndrome, a condition associated with low levels of serum testosterone levels, have been shown to extend beyond cessation of treatment". In p 2360, col. 3, para 2, Mark et al. teaches that "the present data show that exogenous testosterone given for 6 m to men with late onset hypogonadism in doses sufficient to increase serum concentrations does not accumulate in the prostate, does not produce abnormal levels of dihydrotestosterone". It can be evidenced from Mark's teachings that testosterone therapy cannot be implicated as a cancer stimulus and the men who had undergone TRT in 6 m clinical trial do not produce abnormal levels of DHT as to cause prostate cancer. To substantiate Mark's studies, In response to Applicants' stating from the literature that finasteride or dutasteride has an adverse effect of impotence. In response, McConnell et al. teaches a decrease in concentration of dihydrotestosterone and an increase in testosterone concentration after finasteride administration. All treatments with watchful waiting have some risks associated with them. The drugs finasteride, dutasteride are commercially available in the market and the benefits of administering the drug may outweigh the potential adverse effects. In this case, administration of finasteride will decrease the concentration of DHT level and will

increase the amount of testosterone and provide therapeutic benefits in men with metabolic disorders.

Conclusion

No claims are allowed.

Applicant's amendments necessitated the modified rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Umamaheswari Ramachandran whose telephone number is 571-272-9926. The examiner can normally be reached on M-F 8:30 AM - 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/SREENI PADMANABHAN/
Supervisory Patent Examiner, Art Unit 1627